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EXAMINER	
KWON, BRIAN YONG S	

ART UNIT	PAPER NUMBER
1614	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/056,528	HOCHMAN, DARYL W.	
	Examiner	Art Unit	
	Brian S. Kwon	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05/03/06 & Tele. Interview on 06/12/06*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *21,25-29,33,36,37,41,43,45 and 47-53* is/are pending in the application.

4a) Of the above claim(s) *45 47-53* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *21,25-29,33,36,37,41 and 43* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 21, 25-26, 33, 36-37, 41 and 43, drawn to a process of treating migraine headaches and symptoms of migraine headache with the administration of composition consisting of Na+K+2Cl- cotransporter antagonist.

II. Claims 45 and 47-53, drawn to a process of treating migraine headaches and symptoms of migraine headache with the administration of composition consisting of a cation chlorider cotransporter antagonist such as thiazide or thiazide-like composition.

Inventions I and II are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case they have different modes of operation.

"Thiazide and thiazide-like compositions" are distinguished from Na+-K+2Cl- cotransporter such as furosemide and bumetanide because they lack of K+ requirement and insensitivity to sulfamoylbenzoic acid diuretics like bumetanide (see Proc. Natl. Acad. Sci, Vol. 90, pp. 2749-2753, April 1993).

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper.

2. During a telephone conversation with Janet Sleath on June 12, 2006 a provisional election was made with traverse to prosecute the invention of Group I, claims 21, 25-26, 33, 36-37, 41 and 43. Affirmation of this election must be made by applicant in replying to this Office action. Claims 45 and 47-53 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Status of Application

3. Acknowledgement is made of applicants' filing of the instant application as a Request for Continued Examination (RCE) under 37 CFR 1.1114.

4. By Amendment filed April 03, 2006, claims 39, 40, 42, 44 and 56 have been cancelled and claims 21, 27, 45, 47-51 and 53 have been amended. Claims 21,25-29, 33, 36-37, 41, 43, 45 and 47-53 are currently pending for prosecution on the merits.

Response to Arguments

5. Applicant's arguments with respect to claims 21, 23-31, 33 and 35-45 have been considered but are moot in view of the new ground(s) of rejection.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claim 21, 25-29, 33, 36-37, 41, and 43 are rejected under 35 USC 112, first paragraph, because the specification while being enabling for the specific Na+K+2CL- cotransporter such as

furosemide, does not reasonably provide enablement for the term "Na+K+2Cl- cotransporter antagonist that is capable of inhibiting Na+K+2Cl- cotransport in glial cells" (claim 21), "Na+K+2Cl- chloride-dependent cotransporter antagonist blocks spontaneous synchronized deporizing oscillation of neuronal population activity in the central nervous system" (claim 36) or " Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" (claim 37).

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01 (a)). These include: 1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. All the factors have been considered with regard to the claim, with the most relevant factors discussed below.

All rejected claims are drawn to method of treating migraine headache and symptoms of migraine headache in subjects with the administration of said compositions to the subject.

The art recognizes that the cortical spreading depression in involved in pathophysiology of the migraine headache and blocking cortical spreading depression by pharmaceutical agent would be useful in the treatment of migraine headache (WO 95/06468). Furthermore, the

treatment of migraine headache, cortical spreading depression and/or the treatment of migraine by controlling "visual aural" via administering furosemide.

The relative skill of those in pharmaceutical art is high.

The unpredictability of the pharmaceutical art is very high. In fact, the courts have made a distinction between mechanical elements function the same in different circumstances, yielding predictable results, chemical and biological compounds often react unpredictably under different circumstances. Nationwide Chem. Corp. v. Wright, 458 F. supp. 828, 839, 192 USPQ 95, 105(M.D. Fla. 1976); Aff'd 584 F.2d 714, 200 USPQ 257 (5th Cir. 1978); In re fischer, 427 F.2d 833, 839, 166 USPQ 10, 24(CCPA 1970). Thus, the physiological activity of a chemical or biological compound is considered to be an unpredictable art. Likewise, the physiological or pharmaceutical activity of preventing or treating migraine headache, cortical spreading depression and other headache conditions and/or symptoms of such conditions prior to filling of the instant invention was an unpredictable art.

The claims are very broad due to the vast number of possible compounds of that are described as being "Na+K+2Cl- cotransporter antagonist that is capable of inhibiting Na+K+2Cl- cotransport in glial cells to the subject", "Na+K+2Cl- chloride-dependent cotransporter antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system", "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" or "Na+K+2Cl- cotransporter antagonist".

In the instant case, given the unpredictability of the physiological or pharmaceutical activity of the claimed "Na+K+2Cl- cotransporter antagonist" in treating migraine headache,

symptoms of migraine headache is insufficient for enablement. The specification provides no guidance, in the way of enablement for that claimed agent other than furosemide. The specification fails to provide sufficient information or guidance that all compounds that are potentially suitable for the invention work similarly as to furosemide. The skill artisan would have not known that which compounds of the claimed compounds are capable of accomplishing the desired result of the claimed invention without undue amount of experimentation.

In re Fisher, 427 F. 2d 833, 166 USPQ 18 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also In re Wright, 999 F.2d 1557, 27 USPQ2d 1510 (Fed. Cir. 1993); In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991). This is because it is not obvious from the disclosure of one species, what other species will work. In re Dreschfiedl, 110 F. 2d 235, 45 USPQ 36 (CCPA 1940), vies this general rule: "it is well settled that in cases involving chemicals and chemical compounds, which differ radically in their properties it must appear in an applicant's specification either by the enumeration of a sufficient number of the members of a group or by other appropriate language, that the chemicals or chemical combination included in the claims are capable of accomplishing the desired result." The article "Broader than the Disclosure in Chemical Cases," 31 J.P.O.S.5, by Samuel S. Levin covers this subject in detail. A disclosure should contain representative examples, which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See In re Riat et al. (CCPA 1964) 327 F2d 685, 140 USPQ 471; In re Barr et al. (CCPA 1971) 444 F 2d 349, 151 USPQ 724.

As stated above, the instant specification only provides enabling disclosure for the activity of furosemide in inhibiting cortical spreading depression, treating migraine headache, and reducing "visual auras" of migraine (page 5, lines 1-25 of the instant specification).

The quantity of experimentation needed to be performed by one skilled in the art is yet another factor involved in the determining whether "undue experimentation" is required to make and use the instant invention. "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed." In re Wands, 858 F.2d 737, 8 USPQ2d 1404 (citing In re Angstadt, 537 F.2d 489, 502-04, 190 USPQ 214, 218 (CCPA 1976)). For these reasons, one of ordinary skill in the art would be burdened with undue "painstaking experimentation study" to determine all of the agents having "Na+K+2Cl- cotransporter antagonist that is capable of inhibiting Na+K+2Cl- cotransport in glial cells to the subject", "Na+K+2Cl- chloride-dependent cotransporter antagonist blocks spontaneous synchronized depolarizing oscillations of neuronal population activity in the central nervous system", "Na+K+2Cl- chloride-dependent cotransporter antagonist produces modulation of the chloride concentration in extracellular space in the central nervous system" or "Na+K+2Cl- cotransporter antagonist" that would be enabled in this specification.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claim 25-27 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Regarding claims 25 and 26, the phrase "a blood brain barrier permeability enhancer" and "a hyperosmotic agent" renders the claim(s) indefinite because the specification does not define the terms. Thus, such phrases leave the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear. One of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In this regard, although the suitable agents are listed in the specification, for example "leukotrienes, bradykinin agonists, histamine, tight junction disruptors (e.g., zonulin, zot), hyperosmotic solutions (e.g., mannitol), cytoskeletal contracting agents, short chain alkylglycerols (e.g., l-o-pentylglycerol), and others", it is considered that the meaning of the claims should be clear from the wording of the claim alone.

Regarding claim 27, the phrase "furosemide-related compositions" renders the claim(s) indefinite because the claim(s) include(s) elements not actually disclosed (those encompassed by "furosemide-related composition"), thereby rendering the scope of the claim(s) unascertainable.

Independent claim 21 recites "a composition consisting essentially of a Na+K+2Cl- cotransporter antagonist". The recitation of "consisting essentially of" allows for the inclusion of unspecified components which "do not materially affect the basic and novel characteristics of the claimed invention". In other words, the claimed composition cannot contain any components that

affects the basic and novel characteristic of the claimed invention. However, dependent claims 28 and 29 allow for the inclusion of other active ingredients such as anticonvulsant and non-steroidal anti-inflammatory drugs that are known to treat migraine headache and symptoms of migraine headache. This inconsistency leaves the reader in doubt as to the meaning of the invention to which they refer, thereby rendering the definition of the subject-matter of said claims unclear.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

8. Claims 21, 25-29, 33, 36-37, 41 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Read et al. (Cephalalgia, 1997, December, 17(8):826-832) as applied to claims

21, 27, 36 and 37, and further in view of Mathew et al. (Neurology, 1996;46:1226-1230), Levin (US 6432986) and Bentley et al. (US 6369094) and Becker et al. (US 5256687).

Read teaches use of furosemide in non-reactive carrier or hyperosmotic agent such as saline solution, which is a loop diuretic with activity at the electroneutral Na+K+2CL-, in inhibiting regenerative cortical spreading depression in anaesthetized cats, wherein the mechanism of inhibition of cortical spreading depression activity by Na+K+2Cl- cotrasporter or loop diuretics such as furosemide may be through alterations in cortical ion buffering capacity or inhibition of cell swelling in neurons or glia (abstract; page 826, column 1, para. 1-3 thru column 2, para. 1; page 837, column 2, para. 2). Read also teaches that the inhibition of cortical spreading depression is potentially useful for the treatment of migraine therapy (abstract; page 832, column 1, lines 7-11).

Mathew is being supplied as a reference to demonstrate the use of nonsteroidal anti-inflammatory agent, abortive antimigraine agents (e.g., ergotamine, DHE, or sumatriptan), beta blockers, amitriptyline and/or methysergide in combination of furosemide for the treatment of chronic daily headache including migraine headache with or without aura in human (abstract; page 1226, column 2, para. 5 thru page 1228, column 1, para. 4 ; page 1228, column 2, para. 6 thru page 1229, column 1, para. 1; page 1229, column 2, para. 1). The reference discloses that said combination resulted "in the number of days of severe headache, reduced consumption of abortive agents, and overall improvement of quality of life".

Levin is being supplied as a reference to demonstrate the routine knowledge in the art of delivering anti-migraine agents by intranasal and transdermal or topical administration (column 36, lines 31-38; column 9, lines 7-17; column 41, lines 40-43); sustained release formulation,

liposome formulation (column 31, lines 22-31); by implantation or therapeutic device (column 39, lines 3-62). Levin also teaches the use of divalproex sodium for the treatment of migraine headache (column 35, lines 31-32 and column 36, lines 6-7).

Bentley is being supplied as a reference to demonstrate the routine knowledge in the art of delivering anti-migraine agents in various dosage forms including oral, intracvernosal, parenteral (i.e., intracranially), transdermal, ocular and topical administration or controlled released and fast dispersion formulation (column 3, line 8 thru column 4, line 60).

Becker is being supplied as a reference to demonstrate the routine knowledge in the art of using mannitol as pharmaceutical excipient or carrier for furosemide (column 11, line 13).

The teaching of Read differs from the claimed invention in (i) the incorporation of a blood brain barrier permeability enhancer or hyperosmotic agent or solution (claims 25-26 and 33), (ii) the use of one or more agents selected from the group consisting of non-steroidal anti-inflammatory drugs and anticonvulsants such as divalprex sodium (claims 28-29) and (iii) the administration of said composition in various dosage delivery systems including intranasally and intracranially (41 and 43).

However, one having ordinary skill in the art would have known by the art-recognized routine knowledge (Levin Bentley and Becker) that determination of various dosage delivery system or dosage formulation including intranasal, intracranial or transdermal delivery or sustained release formulation, liposome formulation or by implantation or therapeutic device is well within the skill of artisan, especially in migraine therapy art. Furthermore, one having ordinary skill in the art (as taught by Mathew and Levin) would have expected that the incorporation of anti-inflammatory agent and/or anticonvulsant such as divalproex sodium would

provide beneficial effect to the treatment of migraine headache. It is obvious to combine two or more compositions each of which is taught by prior art to be useful for same purpose; idea of combining them flows logically from their having been individually taught in the prior art. The combination of active ingredient with the same character is merely the additive effect of each individual component. *See In re Kerkhoven, 205 USPQ 1069 (CCPA 1980)*. One would have been motivated to combine these references and make the modification because they are drawn to same technical fields (constituted with same ingredients and share common utilities), and pertinent to the problem which applicant concerns about. MPEP 2141.01(a).

With respect to the incorporation of hyperosmotic agent or solution, Becker teaches the use of mannitol as well known secondary agent for furosemide formulation. Thus, one having ordinary skill in the art would have been motivated to combine the references and make such modification to increase the efficacy and extend the usage of furosemide containing composition by making suitable formulation for the claimed invention to accommodate patient's preference and needs where the compliance could be improved with effective and well tolerated dosage regimen.

Conclusion

9. No Claim is allowed.

10. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Kwon whose telephone number is (571) 272-0581. The examiner can normally be reached Tuesday through Friday from 9:00 am to 7:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel, can be reached on (571) 272-0718. The fax number for this Group is (571) 273-8300.

Any inquiry of a general nature of relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications may be obtained from Private PAIR only. For more information about PAIR system, see http://pair-direct.uspto.gov Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll free).

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